

Allylic Dithioacetal as a Propene-1,3-Zwitterion Synthron. Regioselective Conversion of C-S Bonds in Allylic Dithioacetals into C-C Bonds

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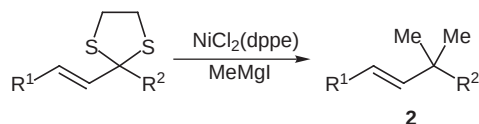
Received 26 January 2001

Dedicated to Professor Ryoji Noyori for his outstanding contribution in organic chemistry

Abstract: Reaction of allylic dithioacetals with organocuprate or organolithium reagent followed by treatment with a variety of alkyl electrophiles gives the corresponding *E* and *Z* isomeric mixture of vinyl sulfides in good yield. Further cross coupling with a Grignard reagent in the presence of $\text{NiCl}_2(\text{dppe})$ affords the corresponding alkylation products in good yield. In general, the Grignard reagent having the same alkyl group as the R^2 substituent in **1** is employed so that the stereochemical problem in coupling products can be lifted.

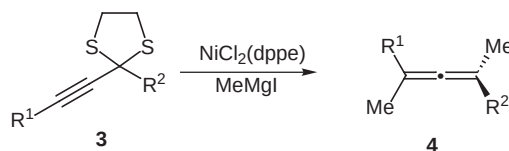
Key words: allylic dithioacetals, organocuprate, electrophiles, cross coupling, zwitterion synthron

Regioselective replacement of a carbon-heteroatom bond in an unsymmetrical allylic system by a carbon-carbon bond is important in organic synthesis. The α - versus γ -selectivity depends on the nature of the substrates, reagents, stoichiometry and reaction conditions.^{1,2} Lewis acids as well as organometallic catalysts occasionally play a pivotal role in directing the regioselectivity. A decade ago, we reported the geminal dimethylation of allylic dithioacetals **1** with MeMgI in the presence of $\text{NiCl}_2(\text{dppe})$ (eq 1).³ No 1,3-dimethylation product was observed at all. On the other hand, propargylic dithioacetal **3** can serve as an allene 1,3-dication synthon **5** leading to 1,3-dimethylation product **4** under similar conditions (eq 2).⁴ More recently, we found that **3** can also behave as an allene 1,3-zwitterion synthon **6** (eq 3).⁵ The interesting feature for this reaction involves an umpolung of one of the two carbon-sulfur bonds in the dithioacetal functionality.⁶ The organocopper intermediate **7** can react with a number of electrophiles leading to either allenyl or alkynyl product **8** or **9**. The regioselectivity of the latter reaction depends on the nature of the electrophile. The remaining carbon-sulfur bond in **8**

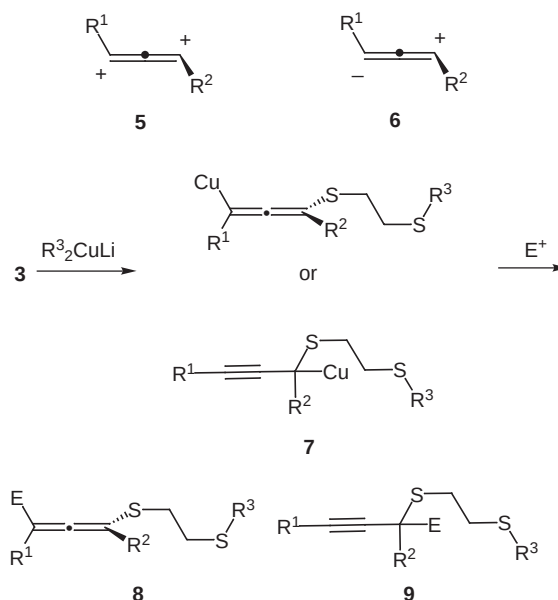


	R^1	R^2
1a	Ph	Me
1b	Ph	Ph
1c	Naph	Me
1d	Naph	Et
1e	Naph	Bu

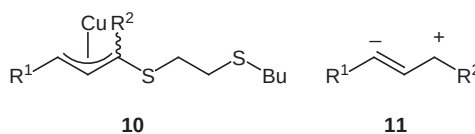
Equation 1



Equation 2

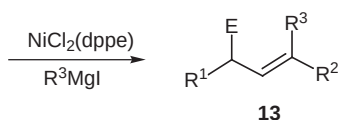
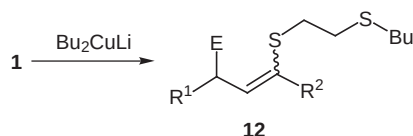


Equation 3



or **9** can be further displaced by the nickel-catalyzed cross coupling reaction.⁷ It is envisaged that the reaction of **1** under similar conditions would generate a substituted allylcopper intermediate **10** which might behave differently from that of the allenyl/propargylic counterpart **7**. We have tested this viewpoint and now wish to report our findings on using allylic dithioacetal as a propene-1,3-zwitterion synthon **11**.

In a typical procedure, reaction of **1** with 0.6 equiv of Bu_2CuLi in THF at -78°C followed by treatment with an alkyl halide afforded regioselectively an *E/Z* mixture of the corresponding vinyl sulfide **12** in good yield (eq 4). Representative examples are summarized in Table 1. Organic lithium reagent (1.2 equiv) behaved similarly (entries 5 and 8–10) and there was no apparent discrepancy in regio- and stereoselectivities whether organocopper reagent or organolithium reagent was employed.



	R ¹	R ²	E	R ³		R ¹	R ²	E	R ³
a	Ph	Me	Me	Me	f	Naph	Me	H	Me
b	Ph	Me	TMSCH ₂	Me	g	Naph	Et	Me	Et
c	Ph	Ph	Me	Me	h	Naph	Et	TMSCH ₂	Et
d	Naph	Me	Bu	Me	i	Naph	Bu	Me	Me
e	Naph	Me	Bn	Me	j	Naph	Bu	TMSCH ₂	Bu

Equation 4

As can be seen from Table 1, a range of alkyl halides can be used for this purpose. The alkyl electrophile reacted regioselectively at the position away from the sulfur substituent of the corresponding unsymmetrical allyl organometallic species **10**. This regioselectivity is just opposite to that observed for the propargylic substrates (eq 3). Presumably, the anionic electron density might be higher at the benzylic position due to resonance. It is interesting to note that, when both C₁ and C₃ positions have aryl substituents, alkylation occurred preferentially at the position having thioether substituent (entry 3). The proton electrophile, however, gave a mixture of regioisomers (entry 6).

The alkylation in general gave a mixture of *E* and *Z* isomeric **12**. Surprisingly, when R² was a methyl group and TMSCH₂Cl was employed as the electrophile, only *E* isomer was isolated (entry 2). The stereoisomers of **12** can sometimes be separated by column chromatography.

By using Wenkert-Takei procedure,⁷ vinylic carbon-sulfur bond can readily be converted into the corresponding carbon-carbon bond. Accordingly, a mixture of *E/Z* isomeric **12** was treated with the Grignard reagent in the presence a catalytic amount of $\text{NiCl}_2(\text{dppe})$ to afford the corresponding coupling product **13** in good yield (eq 4).⁸ In general, the Grignard reagent having the same alkyl group as the R² group in **1** was employed so that the stereochemical problem in **12** can be lifted. The results are tab-

Table 1

entry	Substrate	EX	Product (%yield, <i>E/Z</i>)
1	1a	MeI	12a (79, 1/1)
2	1a	TMSCH ₂ Cl	12b (74, <i>E</i> only)
3	1b	MeI	12c (17, 1/1) ^a
4	1c	BuBr	12d (80, 1/1)
5 ^b	1c	PhCH ₂ Br	12e (70, 4/3)
6	1c	MeOH	12f (40, 1/1) ^c
7	1d	MeI	12g (90, 1/3)
8 ^b	1d	TMSCH ₂ Cl	12h (85, 1/3)
9 ^b	1e	MeI	12i (91, 1/3)
10 ^b	1e	TMSCH ₂ Cl	12j (88, 1/3)

^a**14** was isolated in 60% yield.

^bBuLi was used as the nucleophile.

^c**15** was obtained in 42% yield.

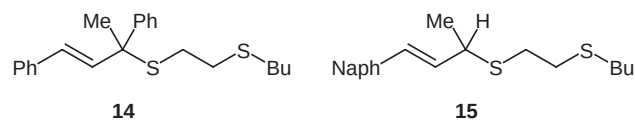
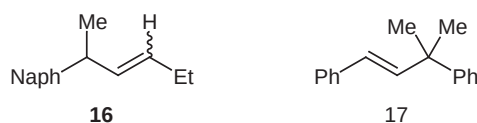


Table 2

entry	Substrate ^a	R ³ MgX	Product (%yield)
11	12a	MeMgI	13a (83)
12	<i>E</i> - 12b	MeMgI	13b (84)
13	12c + 14	MeMgI	13c (80)
14	12d	MeMgI	13d (85)
15	12e	MeMgI	13e (76)
16	12f	MeMgI	13f (88)
17	12g	EtMgBr	13g ^b
18	12h	EtMgBr	13h (85)
19	<i>Z</i> - 12i	MeMgI	13i (88)
20	12j	BuMgBr	13j (87)

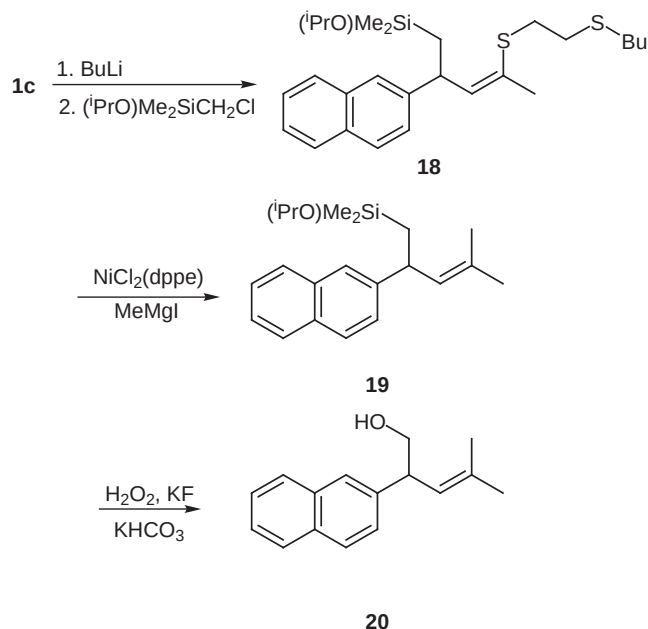
^aUnless otherwise specified, a mixture of *E* and *Z*-**12** was used.

^bAttempts to separate **13g** from the corresponding reduced product **16** were unsuccessful.



ulated in Table 2. It is noteworthy the reaction of a mixture of **12c** and **14** afforded **13c** in good yield (entry 13). Our earlier work showed that the $\text{NiCl}_2(\text{dppe})$ -catalyzed cross coupling of **1b** with MeMgI yields the geminal dimethylation product **17** exclusively.^{3c} The regioselectivity in this study just complements with those of the literature procedures to afford 1,3-dimethylation product **13c** from the same allylic dithioacetal.

The reaction can also proceed in one-pot. Thus, treatment of **1c** with BuLi at $-78\text{ }^{\circ}\text{C}$ followed by $(i\text{PrO})\text{Me}_2\text{SiCH}_2\text{Cl}$ gave the corresponding alkylation product **18** which was allowed to react with MeMgI in the presence of $\text{NiCl}_2(\text{dppe})$ to yield the organosilicon product **19**. Without purification, the crude **19** was oxidized under Tamao conditions⁹ to afford the corresponding alcohol **20**⁸ in 44% overall yield (eq 5).



Equation 5

In summary, we have demonstrated a useful regioselective transformation involving allylic dithioacetals. A variety of electrophiles and alkyl nucleophiles can be used in this strategy. Further investigation on the synthetic applications of this reaction is in progress in our laboratory.

Acknowledgement

We thank the National Science Council and Ministry of Education of the Republic of China for support.

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- (9) ¹H NMR (400 MHz, CDCl_3) data (δ) for selected **13**. **b**: -0.09 (s, 9 H), 0.94 – 1.04 (m, 2 H), 1.66 (s, 3 H), 1.68 (s, 3 H), 3.62 (m, 1 H), 5.25 (br d, $J = 9.2$ Hz, 1 H), 7.12 – 7.28 (m, 5 H). **d**: 0.86 (t, $J = 7.2$ Hz, 3 H), 1.12 – 1.34 (m, 4 H), 1.62 – 1.81 (m, embodied a doublets at 1.68 , $J = 1.2$ Hz and a singlet at 1.71 for the two Me group, 8 H), 3.59 (dt, $J = 9.2$, 7.6 Hz, 1 H), 5.35 (br d, $J = 9.2$ Hz, 1 H), 7.34 – 7.45 (m, 3 H), 7.60 (s, 1 H), 7.75 – 7.79 (m, 3 H). **e**: 1.49 (d, $J = 1.2$ Hz, 3 H), 1.75 (s, 3 H), 2.00 (dd, $J = 13.2$, 8.4 Hz, 1 H), 3.13 (dd, $J = 13.2$, 6.4 Hz, 1 H), 3.93 (m, 1 H), 5.48 (dd, $J = 9.2$, 1.2 Hz, 1 H), 7.11 – 7.23 (m, 5 H), 7.39 – 7.49 (m, 3 H), 7.63 (s, 1 H), 7.77 – 7.83 (m, 3 H). **h**: -0.08 (s, 9 H), 0.92 (t, $J = 7.2$ Hz, 3 H), 0.99 (t, $J = 7.2$ Hz, 3 H), 1.04 (dd, $J = 14.4$, 8.8 Hz, 1 H), 1.12 (dd, $J = 14.4$, 6.8 Hz, 1 H), 2.00 (dq, $J = 7.2$, 1.2 Hz, 2 H), 2.07 – 2.20 (m, 2 H), 3.82 (m, 1 H), 5.30 (br d, $J = 9.6$ Hz, 1 H), 7.35 – 7.43 (m, 3 H), 7.60 (s, 1 H), 7.73 – 7.77 (m, 3 H). **i**: 0.88 (t, $J = 7.2$ Hz, 3 H), 1.23 – 1.42 (m, embodied a doublet at 1.75 , $J = 7.2$ Hz for a Me group, 7 H), 1.67 (d, $J = 1.2$ Hz, 3 H), 2.00 (br t, $J = 7.6$ Hz, 2 H), 3.81 (dq, $J = 9.2$ Hz, $J = 7.2$ Hz, 1 H), 5.35 (dd, $J = 9.2$ Hz, $J = 1.2$ Hz, 1 H), 7.36 – 7.45 (m, 3 H), 7.64 (s, 1 H), 7.75 – 7.77 (m, 3 H). **j**: -0.06 (s, 9 H), 0.90 (t, $J = 7.2$ Hz, 6 H), 1.05 (dd, $J = 14.4$, 8.0 Hz, 1 H), 1.15 (dd, $J = 14.4$, 6.8 Hz, 1 H), 1.24 – 1.41 (m, 8 H), 1.96 – 2.00 (m, 2 H), 2.08 – 2.12 (m, 2 H), 3.84 (m, 1 H), 5.38 (br d, $J = 9.2$ Hz, 1 H), 7.38 – 7.46 (m, 3 H), 7.62 (s, 1 H), 7.75 – 7.80 (m, 3 H). **20**: 1.72 (d, $J = 1.2$ Hz, 3 H), 1.78 (d, $J = 0.8$ Hz, 3 H), 3.74 – 3.93 (m, 3 H), 5.44 (br q, $J = 9.2$ Hz, 1 H), 7.36 – 7.48 (m, 3 H), 7.67 (s, 1 H), 7.77 – 7.81 (m, 3 H).
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Article Identifier:

1437-2096,E;2001,0,SI,0977,0979,ftx,en;Y03101ST.pdf